CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-014

PROPRIETARY NAME REVIEW(S)

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
HFD-420; White Oak Building #22, Mail Stop 4447

DATE RECEIVED: November 20, 2006	**DESIRED COMPLETION DATE:** February 20, 2007	**OSE REVIEW #:** 2006-872
DATE OF DOCUMENT: September 28, 2006	**PDUFA DATE:** July 29, 2007	

TO: Scott Monroe, MD
Acting Director, Division of Reproductive and Urologic Products
HFD-580

THROUGH: Linda Y. Kim-Jung, PharmD, Team Leader
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FROM: Todd Bridges, RPh, Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME: **Evamist** (Estradiol Transdermal Spray) 1.53 mg/spray **NDA #:** 22-014	**SPONSOR:** Vivus, Inc.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Evamist. DMETS considers this a final review. However, if approval of the application is delayed beyond 90 days from the signature date of this review then the name and its labels and labeling must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of this product.

3. DDMAC finds the proposed proprietary name, Evamist, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. Please copy DMETS on any correspondence to the sponsor pertaining to this review. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Cherye Milburn, OSE Project Manager, at 301-796-2084.

Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
HFD-420; White Oak Building #22, Mail Stop 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL, AND LABELING REVIEW

DATE OF REVIEW: January 23, 2007

NDA #: 22-014

NAME OF DRUG: **Evamist**
(Estradiol Transdermal Spray)
1.53 mg/spray

NDA HOLDER: Vivus, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Products (HFD-580), for assessment of the proprietary name, Evamist, regarding potential name confusion with other proprietary or established drug names. Container label, carton and insert labeling were submitted for review and comment at this time.

PRODUCT INFORMATION

Evamist (Estradiol Transdermal Spray) is a transdermal estrogen spray being developed for the treatment of moderate to severe vasomotor symptoms associated with menopause. The recommended dosage regimen is one to three sprays applied once daily to adjacent, non-overlapping areas of the forearm. Evamist will be supplied in a glass vial fitted with a metered dose pump which is encased in a plastic housing. Each vial contains 8.1 mL of solution that yields 56 metered sprays; each spray contains 1.53 mg of Estradiol.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of the internet, several standard published drug product reference texts[1,2] as well as several FDA databases[3,4] for existing drug names which sound-alike or look-alike to Evamist to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. The Saegis[6] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name. Following completion of these initial components, an overall risk assessment is conducted that does not evaluate the name alone. The assessment considers the findings from above and more importantly integrates post-marketing experience in assessing the risk of name confusion, product label/labeling, and product packaging. Because it is the product that is inserted into the complex and unpredictable U.S. healthcare environment, all product characteristics of a drug must be considered in the overall safety evaluator risk assessment.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Evamist. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proposed proprietary name, Evamist, acceptable from a promotional perspective.

2. The Expert Panel identified three proprietary names that were thought to have the potential for confusion with Evamist. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

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[1] MICROMEDEX Integrated Index, 2007, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-07, and the electronic online version of the FDA Orange Book.

[4] Phonetic and Orthographic Computer Analysis (POCA)

[5] WWW location http://www.uspto.gov/tmdb/index.html.

[6] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Look-Alike Names Identified by DMETS Expert Panel.

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Evamist	Estradiol Transdermal Spray 1.53 mg per actuation	One to three sprays applied once daily to adjacent, non-overlapping areas of the forearm.	
Alamast	Pemirolast Potassium Ophthalmic Solution 0.1%	1 to 2 drops in affected eye(s) four times daily.	L/A
Alavert	Loratadine Tablets 10 mg	1 tablet daily.	L/A
Avonex	Interferon beta-1a Powder for injection, lyophilized: 33 mcg (6.6 million units [30 mcg/vial when reconstituted]) and Prefilled syringe: 30 mcg per 0.5 mL	30 mcg intramuscularly once a week.	L/A
*Frequently used, not all-inclusive. **L/A (look-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Evamist with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. Each study employed a total of 119 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Evamist (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Evamist #1 One spray daily	Evamist 1 spray daily Dispense 1
Inpatient RX: Evamist 1 Spray Daily	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See Appendix A (page 11) for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

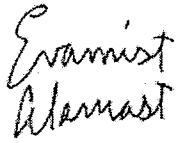
In reviewing the proposed proprietary name, three names were identified as having either a similar appearance and/or sound to Evamist. These names are Alamast, Alavert, and Avonex. Upon review of these names, Alavert and Avonex were not considered further because they lack convincing look-alike similarities with Evamist in addition to having numerous differentiating product characteristics such as the product strength, dosage form, and indication for use. Additionally, Alavert is an over-the-counter product.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Evamist.

The remaining name with potentially similar appearance, Alamast, is discussed in detail below.

Alamast was identified as having look-alike similarities with the proposed name, Evamist. Alamast (pemirolast potassium) is an ophthalmic solution indicated for the prevention of itching of the eye due to allergic conjunctivitis. The recommended dose is 1 to 2 drops instilled into the affected eye(s) 4 times daily.

The orthographic similarities between Alamast and Evamist can be attributed to similar suffixes ("-amast" vs. "-amist") which may look-alike when scripted. Additionally, the letters "e" and "a" can resemble one another if scripted using a lower case letter,



However, these drug names are distinguished from one another by different initial capital letters ("A" vs. "E") and the additional upstroke letter ("l") of Alamast. Additionally, Alamast and Evamist vary with regards to dosage form (ophthalmic solution vs. topical spray), route of administration (opthalmically vs. topically), frequency of administration (4 times daily vs. once daily), and strength (0.1% vs. 1.53 mg). Although Alamast and Evamist differ in product strength, the strength may be omitted on a prescription since each drug is only available in a single strength. However, a prescription for either medication will likely include the frequency of administration which may help to differentiate these products from one another. Additional distinguishing information such as "gtt(s)" and "spray(s)" may also be included in the directions for use on an order for Alamast and Evamist, respectively. Furthermore, a prescriber ordering Alamast will usually indicate the affected eye(s) by inclusion of "OS", "OD" or "OU" in the directions for use. If included on a prescription for Alamast, these Latin abbreviations may lessen any confusion stemming from similarities involving this name pair. Overall, differing product characteristics such as the dosing interval and orthographic differences in the beginnings of the names ("Al" vs. Ev") will help to minimize the potential for confusion and error between Alamast and Evamist.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container label, carton and insert labeling of Evamist, DMETS focused on safety issues relating to medication errors. However, copies of the label and labeling were provided in black and white, and may not represent the true color of the label and labeling. Therefore, DMETS cannot assess if there are any safety concerns due to the colors utilized on the label and labeling. Please forward copies of the revised label and labeling, in color and reflective of the presentation that will actually be used in the marketplace, when they are available. Upon review of the draft black and white label and labeling, DMETS has identified the following areas of improvement, in the interest of minimizing user error and maximizing patient safety.

A. GENERAL COMMENTS

1. Ensure that the proprietary and established names are the most prominent information on the labels and labeling. Additionally, ensure that the established name is at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2).

2. The proposed proprietary name is presented in script font which is difficult to read and may lead to misinterpretation of "Evamist" as "Evavist". Revise so that the proposed proprietary name appears in a print font. Additionally, delete the tallman lettering used for the letter "m" in the proprietary name. The use of tallman letters should be reserved for names with known potential for confusion; using a capital letter "m' may also overemphasize the "mist" portion of the proprietary name.

3. Revise the statement of product strength to read "1.53 mg/spray" and relocate so that it appears directly below the established name. For example:

Evamist
(Estradiol Transdermal Spray)
1.53 mg/spray

4. Relocate the net quantity statement (8.1 mL) so that it appears away from the product strength, preferably at the bottom of the principal display panel. This should aid in decreasing the risk of confusion between the net quantity and the product strength.

5. DMETS recommends that the abbreviation "µL" be revised to read "mcL" throughout the labels and labeling. FDA launched a campaign on June 14, 2006, warning health care providers and consumers not to use error-prone abbreviations, acronyms, or symbols (e.g., mu symbol). Thus, we request that the Divisions not approve or use such symbols in their labels and labeling. We further note that the use of the mu symbol (e.g., µL for micro liter) is specifically listed as a possibly dangerous abbreviation, acronym, or symbol in the 2006 National Patient Safety Goals of The Joint Commission for Accreditation of Hospitals (JCAHO). Lastly, safety groups, such as the Institute for Safe Medication Practices (ISMP), also list the mu symbol on their dangerous abbreviations and dose designations list.

6. The sponsor states that each pump is designed to deliver "fifty-six 90 µL sprays". Revise this description to read "Delivers 56 sprays. Each spray delivers 1.53 mg of Estradiol." since "90 µL" does not covey any useful information to healthcare professionals or patients and may create confusion.

B. CONTAINER LABEL

1. See GENERAL COMMENTS A1 through A6.

2. Revise to include a "Rx Only" statement on the bottom third of the principal display panel.

3. Revise so that "For Topical Use Only" appears as a stand alone statement and not imbedded in the text that follows. For example,

For Topical Use Only

Each spray delivers....

C. CARTON LABELING

1. See GENERAL COMMENTS A1 through A6.

2. Relocate the route of administration statement "For Topical Use Only" to the primary display panel.

3. "Dosing Instructions:" on side panel:

   The dosing instructions that appear on the side-panel are abbreviated and ambiguous. For example, the sponsor has failed to include instructions for patients having difficulty applying the prescribed dose to distinct, non-overlapping areas of the same forearm. Additionally, the sponsor states "Allow the sites to dry for 2 minutes before covering with clothing and do not wash the sites for 30 minutes after application." This statement may be misconstrued by patients to mean that the area must be occluded (i.e., covered with clothing) following Evamist application. It would be best to refer to the full instructions for use. If full directions can not be placed on the carton, then the abbreviated version should be deleted because they may be misinterpreted.

4. Relocate the statement which begins "The metered-dose pump is...." to the primary display panel. This statement should be followed by the statement "Each spray delivers 1.53 mg of Estradiol."

5. Relocate the statement which begins "The metered-dose pump is...." to the primary display panel. This statement should be followed by the statement "Each spray delivers 1.53 mg of Estradiol."

6. Relocate the storage statement '[redacted] to the side panel since it may be inadvertently covered by the pharmacy label in its current location. Additionally, so that all storage statements are together, list the aforementioned statement with the statement "Do not freeze." b(4)

D. PACKAGE INSERT LABELING

1. See GENERAL COMMENTS A2 and A5.

2. DOSAGE AND ADMINISTRATION

   Revise the statement "One, two, or three sprays are applied daily ...." to include the phrase "as directed by your physician". For example,

   "One, two, or three sprays (as directed by your physician) are applied daily...."

3. DOSAGE FORM AND STRENGTH

   In the statement "Each spray of the metered dose pump delivers 90 µL (1.53 mg of estradiol).", stating the volume of medication delivered in each spray (i.e., 90 µL) does not convey useful information to the healthcare practitioner and may cause

confusion. Revise to read "Each spray of the metered dose pump delivers 1.53 mg of estradiol."

4. HOW SUPPLIED/STORAGE AND HANDLING

   a. Delete the phrase ' [redacted] as this implies that there is more than one dosage form of Evamist available. b(4)

   b. Revise this section to include the net quantity statement (i.e., 8.1 mL) and the number of sprays in each container (i.e., 56 sprays).

E. PATIENT PACKAGE INSERT LABELING

1. See GENERAL COMMENT A2.

2. How should I use Evamist?

   Under instruction #6, revise the statement "Simply allow the spray…" to read "Allow the spray to dry for at least 2 minutes and do not wash the site(s) for at least 30 minutes after application." as "before dressing" may be misconstrued by patients to mean that the area must be occluded following Evamist application.

APPEARS THIS WAY ON ORIGINAL

Appendix A. Evamist Prescription Study Results

Inpatient	Outpatient	Voice
Evamist	Evamist	Evamist
Evamist	Evamist	evamist
Evamist	evamist	Evamist
Evamist	EVAMIST	Evamist
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